Elsevier Editorial System(tm) for Joint Bone Spine
Manuscript Draft

Manuscript Number:

Title: Evaluation of the immunogenicity of the 13-valent conjugated pneumococcal vaccine in rheumatoid arthritis patients treated with etanercept

Article Type: Original article

Keywords: rheumatoid arthritis; vaccination; biological therapy; etanercept; Pneumococcus

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Manuscript Region of Origin: HUNGARY

Abstract: Objectives: To prospectively evaluate the immunogenicity of a 13-valent conjugated pneumococcal vaccine (PCV13) in rheumatoid arthritis (RA) patients undergoing etanercept therapy.
Methods: Twenty-two RA patients treated with etanercept (ETA) in combination with methotrexate (MTX) (n=15) or monotherapy (n=7) for at least one year were included. Altogether 24 osteoarthritis patients not receiving biological or MTX therapy, treating only NSAIDs or analgesics served as controls. All subjects were vaccinated with a single dose (0.5 ml) of the PCV13. Pneumococcal antibody levels at baseline, 4 and 8 weeks were assessed by a VaccZymeTM Anti-PCP IgG Enzyme Immunoassay Kit. Based on recommendations of the American Academy of Allergy, Asthma & Immunology, an at least twofold increase in antibody level, as the protective antibody response (pAR) was an indicator of responsiveness (i.e., ratio of postvaccination and prevaccination antibody levels). The antibody levels and their ratios were analysed in a variety of different ways, vaccine safety parameters (fever, infections, changes in regular antirheumatic treatments) were assessed at baseline, 4 and 8 weeks after vaccination.
Results: Four weeks after vaccination, the anti-pneumococcal antibody levels significantly increased in both groups. At week 8, antibody levels somewhat decreased in both groups, however, still remained significantly higher compared to baseline. Compared with postvaccination levels at 4 and 8 weeks between two groups, the mean protective antibody levels were higher in control group (1st month p=0.016; 2nd month: p=0.039). Possible predictors of pAR were analysed by logistic regression model. In RA, increases of antibody levels at week 8 compared to baseline exerted a negative correlation with age, (Spearman's R=-0,431; p=0.045). There were no clinically significant side effects or reaction after administration of vaccine observed in any of these patients after the 2-month follow-up period, all patients medical condition were stable.
Conclusions: In RA patients treated with ETA, vaccination with PCV13 is effective and safe, resulting in pAR one and two months after vaccination. Higher age at vaccination was identified as predictors of impaired pAR. The efficacy of vaccination may be more pronounced in younger RA patients. The vaccine is safe in RA patients on ETA.

Evaluation of the immunogenicity of the 13-valent conjugated pneumococcal vaccine in rheumatoid arthritis patients treated with etanercept

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ABSTRACT

Objectives: To prospectively evaluate the immunogenicity of a 13-valent conjugated pneumococcal vaccine (PCV13) in rheumatoid arthritis (RA) patients undergoing etanercept therapy.

Methods: Twenty-two RA patients treated with etanercept (ETA) in combination with methotrexate (MTX) (n=15) or monotherapy (n=7) for at least one year were included. Altogether 24 osteoarthritis patients not receiving biological or MTX therapy, treating only NSAIDs or analgesics served as controls. All subjects were vaccinated with a single dose (0.5 ml) of the PCV13. Pneumococcal antibody levels at baseline, 4 and 8 weeks were assessed by a VaccZyme^{TM} Anti-PCP IgG Enzyme Immunoassay Kit. Based on recommendations of the American Academy of Allergy, Asthma & Immunology, an at least twofold increase in antibody level, as the protective antibody response (pAR) was an indicator of responsiveness (i.e., ratio of postvaccination and prevaccination antibody levels). The antibody levels and their ratios were analysed in a variety of different ways, vaccine safety parameters (fever, infections, changes in regular antirheumatic treatments) were assessed at baseline, 4 and 8 weeks after vaccination.

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Keywords: rheumatoid arthritis, conjugated pneumococcal vaccine, PCV13, etanercept, protective antibody level

INTRODUCTION

In 2012, lower respiratory tract infections affected 3.1 million people and thus became the 4th most common cause of death according to the World Health Organisation (1). The deaths due to pneumonia are 2–5-times more common than in the general population (2, 3). *Streptococcus pneumoniae* (*S.pneumoniae*) is the most common cause of pneumonia in the community, as well as in hospital inpatients. The most important virulence factors of *S. pneumoniae* are capsular serotypes (4). From the known 90 serotypes globally only 20 serotypes are responsible for more than 80% of invasive pneumococcal diseases in all age groups (5). These serotypes causing invasive diseases differ from country to country. The role of these serotypes and their follow up are essential for development of the new generation of conjugate vaccines (6).

A 23-valent pneumococcal polysaccharide vaccine (PPV23) licensed in 1983 (7) is less immunogenic, than newly developed conjugated vaccines (PCV7, PCV10, PCV13). These new vaccines due to T-cell dependent immune responses induce high level of memory B-cells to trigger the creation of an immunological memory (8). Two conjugated vaccines, a 7-valent and a 10-valent one were approved by FDA in 2000 and 2009, respectively, to be applied only to infants and children (9, 10). Infections caused by Gram positive bacteria, *S. pneumoniae* are vaccine-preventable diseases, but the efficacy of vaccination may be problematic in immunocompromised patients, in particular in autoimmune rheumatological disease (AIRD) and elderly patients (11, 12, 13, 14). However, the use of immunosuppressive drugs, such as anti-TNF biologics may mildly-moderately impair the host response to various vaccines against pneumococcal, influenza and other infections (15, 16).

Kapatenovic et al (16, 9, 9, 12) investigated the 7-valent conjugated pneumococcal vaccine in adult RA patients treated with ETA. These studies have shown protective immune response using PCV7 vaccine. Only 20.5% of patients exerted decreased antibody levels after 1.5 year-follow-up period. PCV7 vaccine has been approved for only children but its use has never been recommended in adult populations, and there is no clinical evidence for use in adults. The other 10-valent PCV vaccine has never been licensed and investigated in adults.

Whereas PCV7 did not cover for some most important serotypes (serotypes 1, 5 and 6A), thus it has not been used since March 2010 and has been broadly replaced by higher valency conjugate vaccine (PCV13) as World Health Organization recommended (17).
In 2011 FDA licensed the 13-valent pneumococcal conjugate vaccine (PCV13) for prevention of pneumonia and invasive diseases in adults aged ≥50 years (18), than 2012 the ACIP recommended the routine use of PCV13 for adults with immunocompromised conditions (19). In a recently published randomized, double-blind, placebo-controlled trial including 84,496 adults (65 years of age or older) the efficacy of PCV13 in preventing vaccine-type pneumococcal, bacteremic, and nonbacteremic community-acquired pneumonia and vaccinetype invasive pneumococcal disease was confirmed (20).

There has been no available information with respect to the efficacy and safety of the PCV13 vaccine in immunocompromised patients in particularly anti-TNF-treated RA patients. The primary objective of our investigation was to compare immunologic responses for PCV13 between RA patients treated with ETA and patients suffering from osteoarthritis served as control group. Based on recommendations of the American Academy of Allergy, Asthma & Immunology (21), an at least twofold increase in antibody level was an indicator of protective anitibody responsiveness (i.e., ratio of postvaccination and prevaccination antibody levels). The secondary objective was to show the safety of this vaccine in this group.

PATIENTS AND METHODS

Altogether 22 RA patients (17 females, 5 males, mean age 55.1±10.4 years) undergoing current treatment with the recombinant TNF-α receptor fusion protein ETA at the University of Debrecen, Faculty of Medicine, Department of Rheumatology were included into this prospective observational study. All RA patients had been treated with 50 mg ETA administered SC once a week for at least one year. Out of these 22 patients, 15 patients received combination therapy of ETA+MTX (the mean MTX dose was 12.3±4.5 mg/week), while 7 patients received ETA monotherapy only. Five patients received corticosteroids in RA group (4 patients in the ETA+MTX combined group) at a mean dose of 2.8 ±1.1 mg/day. There were no other type of DMARDs therapy administered to the patients. Mean DAS28

(CRP) indicated low disease activity in most of patients (2.78 ± 0.62) at baseline, before vaccination.

A control group of 24 patients with osteoarthritis (OA) (18 females, 6 males; mean age 63.9±9.7 years) was also established. Control subjects did not receive any immunosuppressive agents, they were only NSAIDs and analgetics. The clinical data of RA and OA patients are included in Table 1. All patients in the study groups were pneumococcal vaccine naïve (never vaccinated with any pneumococcal vaccines). Exclusion criterias included primary immunodeficiency, as well as other chronic autoimmune-rheumatic diseases and diabetes mellitus, chronic hepatitis, malignancy, bronchial asthma, alcoholism, splenectomy in order to exclude the most common causes of other secondary immunodeficiency that may influence of antibody response for vaccination in RA or control group. All patient of both groups has immunoglobulin levels (IgA, IgG and IgM) in a normal ranges. Control patients more frequently had cardiovascular disease (coronary heart disease, hypertension) than RA patients (Table 1); metabolic (hyperlipidaemia, obesity) and gastrointestinal (duodenal ulcer, gastro-esophageal reflux) co-morbidities did not differ significantly in the two groups. PCV13 vaccination was performed in all RA patients 5 days before administering the next dose of etanercept. The vaccination was performed in written consent of patients and contraindication checklist.

All subjects were vaccinated with a single dose (0.5 ml) of the PC13 vaccine (Prevenar 13, Pfizer) IM into the upper arm. Total anti-PPV23 antibody levels produced against the various serotypes were measured. Pre-vaccination anti-PPV23 levels were compared to those 4 weeks and 8 weeks after vaccination. Pneumococcal antibody levels were assessed by a VaccZyme^{TM} Anti-PCP IgG Enzyme Immunoassay Kit. According to recommendations of the American Academy of Allergy, Asthma & Immunology, an at least twofold increase in antibody level was an indicator of good responsiveness (21). An Institutional Review Board approval had been obtained before the initiation of the study.

Statistical analysis was performed using the SPSS 20 software. Data are presented as mean values and standard deviation (SD). The normality of continuous variables was evaluated by the Kolmogorov-Smirnov test. Data obtained in the RA and control groups were compared by independent t-test, Mann-Whitney U test, chi^2 test or Fisher's exact test. Correlations were determined by Spearman's test. In all statistical tests p values < 0.05 were considered significant.

RESULTS

Antibody responses

Clinical and epidemiological data of the two patient groups are shown in Table 1.

At baseline, pneumococcal antibody levels (IgG t=0) in RA patients and in controls were 110.1±68.2 mg/l and 124.0±99.0 mg/l, respectively (Table 2). Baseline levels in two groups did not show statistically significant difference. One month after vaccination, antibody levels (IgG t=1) increased in both groups (RA: 247.7±155.6 mg/l; controls: 417.7±198.3 mg/l) compared to baseline ($p<0.001$). The mean increase in antibody levels between baseline and 4 weeks were 2.63-fold in the RA and 6.13-fold in the control group ($p=0.016$). There was also significant difference between the two groups. After two months, antibody levels (IgG t=2) somewhat decreased in both groups, however, still remained significantly higher compared to baseline (RA: 207.6±127.6 mg/l; control: 356.4±171.2 mg/l). The mean increase in antibody levels after 8 weeks were 2.08-fold and 5.2-fold in the RA and control groups, respectively, compared to baseline (Figure 1, Table 2).

When comparing RA patients receiving ETA-MTX combination (n=15) and ETA monotherapy (n=7), the subgroup treated with combination produced higher rate of increase in pneumococcal antibody levels after one month (2.89-fold increase) in comparison to the ETA monotherapy group (2.07-fold increase), however, the difference was not statistically significant ($p=0.503$). After 2 months, the combination and monotherapy groups exerted 2.22-fold and 1.76-fold increases in antibody levels, respectively, the difference between the two subgroups was not significant ($p=0.245$).

Pneumococcal antibody levels were analyzed in a variety of different ways. As indicated in Figure 2, in the RA group, the increase in antibody levels between week 8 and baseline significantly, negatively correlated with age (Spearman's R=-0,431; $p=0.045$). Such correlation was not observed in the control group.

Vaccine safety and side effects

In RA group MTX treatment was stopped in 2 patients due to gastrointestinal side effect 1 month after vaccination, otherwise their condition was stable and they did not need any supplementary treatment. In control group there were no any changes in regular medications within 2 months after the PCV13 administration. During the post-vaccination follow-up period patients had no complaint; fever or pain or any infection, or any changes in

their medical condition. Summarized, there were no clinically significant side effects or any reaction observed in any of these patients within the 2-month follow-up period.

DISCUSSION

Until now, no data on the immunogenicity of PCV13 in anti-TNF-treated RA patients have become available. In the light of this, we evaluated the immunogenicity and safety of the new conjugated, 13-valent pneumococcal vaccine in RA patients undergoing ETA therapy. Clinically significant (>2-fold) elevations of antibody levels as protective level were observed after one and two months post-vaccination compared to baseline in both RA and control groups. Four weeks after vaccination, antibody levels significantly increased in both groups. Antibody levels somewhat decreased by week 8 in both groups, however, these levels still remained significantly higher compared to baseline antibody concentrations.

After approval of standard 23-valent polysaccharide vaccine both in children and adults (23, 9, 7) and then heptavalent conjugate vaccines only in children (16, 9), in 2010, a new, more immunogenic 13-valent pneumococcal conjugate vaccine (PCV13) was introduced (23). PCV13 has been effectively administered to subjects over the age of 50 (18). Since 2012, this vaccine has also been recommended by the American Advisory Committee on Immunization Practices (ACIP) to immunosuppressed patient for administering at any age (19). This is the first conjugate pneumococcal vaccine approved for adults. There have been only a very limited number of publications on the immunogenicity and efficacy of standard 23-valent polysaccharide and heptavalent conjugate pneumococcal vaccines in biologic-treated RA patients. These reports suggested that similar or only mildly affected immune responses were detectable in anti-TNF biologic-treated versus non-treated patients (11, 16, 23, 9, 24)

Our results showed that higher age was associated with poorer antibody responses at week 8 in the RA group. This correlation was not seen in control group despite significantly older age of OA group, than RA group. This association was also reported previously by others (9, 25, 26) . These results suggested, that immunresponse of RA patients may be affected by basic autoimmune rheumatic disease considering pathologic functions of B cells to produce antibodies (27).

We observed non-significantly better responses to PCV13 in patients receiving ETA-MTX combination compared to ETA monotherapy, but it is difficult to draw any conclusions regarding the actual effect of etanercept itself, because the group sizes of ETA versus ETA+MTX are too small. Although MTX itself may impair immune responses to pneumococcal vaccines (PPV3 and 7-valent PCV) resulted in earlier studies (16, 23), this issue should be studied closer in a larger patient group after PCV13 administration.

Our study had several limitations. The study was performed in a single centre in Hungary. RA patients treated with only DMARDs especially on MTX alone were not included in the study, because the number of these patients at our department is limited, and the combined DMARDs therapy would not have reflected the exact difference between groups. Another control group of RA patients on other therapies would have been useful, e.g. a drug free RA group would be ideal, but infeasible for this purpose. We did not want to have a patient population treated with different biologics.
The number of patients within RA group, especially in the combination versus monotherapy subgroups are relatively low. However, it has not been easy to do an at least two months prospective vaccination study using ETA only. In addition, the control OA group could not be fully matched to the RA group with respect to age. Moreover, the post-vaccination follow-up period was not enough to determine antibody response on a long-term basis. The duration of protection after PCV13 vaccination is still unknown, but it probably lasts at least several years.

In conclusion, this study is the first to demonstrate that PCV13 vaccination of RA patients undergoing ETA therapy may not impair antibody response after 2 months of vaccination. The administration of PCV13 was effective and safe, resulting in an at least two-fold increase in pneumococcal antibody levels after 2-month follow-up period. The efficacy of this conjugated pneumococcal vaccination may be more pronounced in younger RA patients. Our results showed, that the newly approved for adults pneumococcal vaccine can be used in RA patients treated with ETA safely and effectively. Pneumococcal vaccination is very important and a critical part of RA patients' clinical management. Further research including larger groups of patients treated with biologics given as monotherapy and in combination with conventional DMARDs are needed to determine the benefit of conjugated pneumococcal vaccination administration in patients with RA and other inflammatory rheumatic diseases.

ACKNOWLEDGEMENTS

This work was supported by the TÁMOP 4.2.4.A/2-11-1-2012-0001 National Excellence Program co-financed by the European Union and Hungary (Z.S.); by research grant TÁMOP-4.2.2.A-11/1/KONV-2012-0031 financed by the European Union (Z.S.); and by a Bridging Fund from the University of Debrecen Faculty of Medicine (Z.S.).

FIGURE LEGENDS

Figure 1. Pneumococcal antibody levels at baseline (IgG 0) and one month (IgG 1) and two months (IgG 2) after vaccination.

Figure 2. Correlation between age and rate of changes of pneumococcal antibody IgG levels (IgG 2/IgG 0) in RA patients.

Table 1 Epidemiological data of patients

	RA group	Control group	p
All patients (n)	22	24	1.00
Male	5	6	
Female	17	18	
Mean age (year)	55.1 ± 10.4	63.9 ± 9.8	***0.005***
Male	52.0 ±11.1	61.3 ±12.5	0.226
Female	56.1 ± 10.3	64.8 ± 8.9	***0.011***
Co-morbidities (n) Cardiovascular Metabolic Gastrointestinal	 12 (55 %) 6 (27%) 8 (36%)	 20 (83 %) 9 (36 %) 6 (25 %)	 ***0,034*** 0.460 0.403
Treatment (n)			
Etanercept + MTX	15 (68 %)	0	-
Etanercept + MTX + steroids	4 (18 %)	0	
Etanercept monotherapy	7 (32 %)	0	-
Etanercept + steroids	1 (5%)	0	
Immunserological tests			
Rheumatoid factor positive	13 (59 %)	0	-
ACPA positive	11 (50 %)	0	-
Disease activity			-
DAS 28 (CRP)	2,78 ± 0,62	-	-

Table 2 Serum pneumococcal antibody level at baseline, after one and two months

PATIENTS	PNEUMOCOCCAL ANTIBODY LEVELS (MG/L)			RATE OF CHANGES OF IgG LEVELS		
	IgG t=0 baseline	**IgG t=1**	**IgG t=2**	**0-1 month**	**0-2 months**	**p**
RA (n=22)	110.1±68.2	247.7±155.2	207.6±127.6	2.6-fold (±1.5) increase	2.08-fold (±0.87) increase	***<0.001***
Control (n=24)	124.0±99.0	417.7±198.3	356.4±171.7	6.13-fold (±7.3) increase	5.20-fold (±5.32) increase	***<0.001***
p	0,585	***0,002***	***0,002***	***0.016***	***0.039***	

IgG t=0, baseline pneumococcal antibody level; IgG t=1, pneumococcal antibody level after one month; IgG t=2, pneumococcal antibody level after two months

Table 3 The effect of etanercept-MTX combination vs etanercept monotherapy on antibody response

TREATMENT	PNEUMOCOCCAL ANTIBODY LEVELS (MG/L)			RATE OF CHANGES OF IgG LEVELS	
	IgG t=0 baseline	**IgG t=1**	**IgG t=2**	**0-1 month**	**0-2 months**
Combination (n=15)	103.6±63.9	263.8±179.2	217.0±143.7	2.89-fold (±1.75) increase	2.22-fold (±0.94) increase
Monotherapy (n=7)	123.9±80.2	213.0±86.1	187.3±89.9	2.07-fold (±0.73) increase	1.76-fold (±0.65) increase
p	0.531	0.488	0.622	0.503	0.245

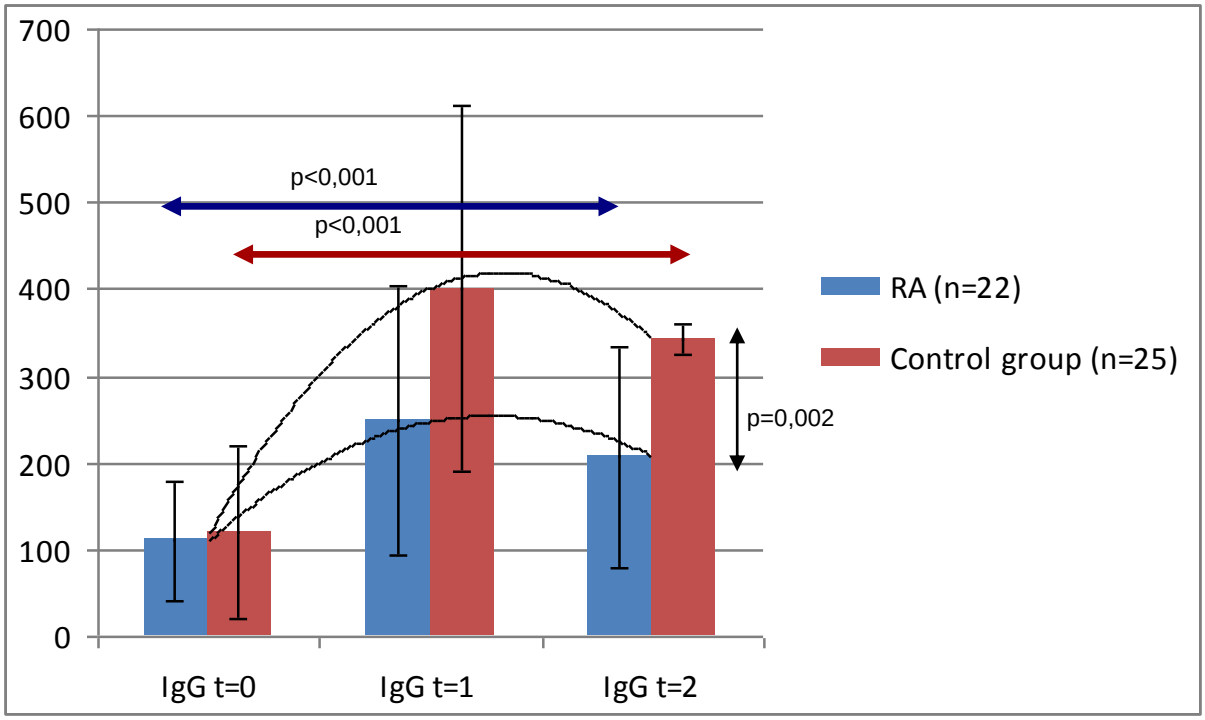
700
600
500
400
300
200
100
0
p<0,001
p<0,001
p=0,002
RA (n=22)
Control group (n=25)
IgG t=0
IgG t=1
IgG t=2

Figure 1.

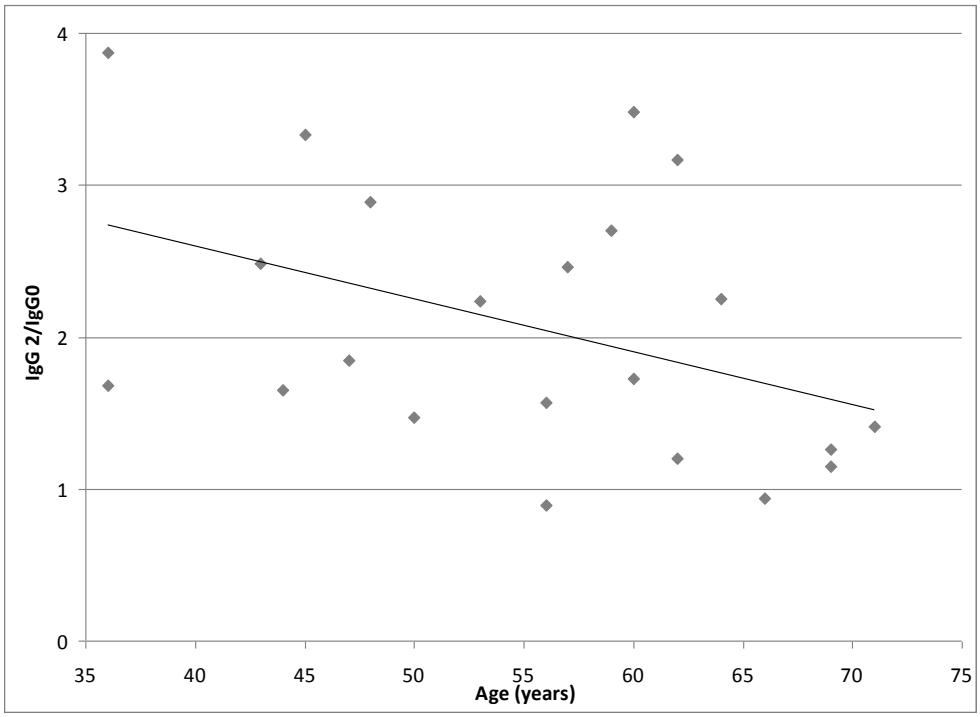

Figure 2

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